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Preplaque ('preclinical') A -induced inflammation and nerve growth factor deregulation in transgenic models of Alzheimer's disease-like amyloid pathology

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Abstract: BACKGROUND: Alzheimer's disease (AD) neuropathology likely begins decades before clinical symptoms are manifested. Investigations on the early stages of the amyloid pathology are crucial for the discovery of diagnostic biomarkers or new therapeutic targets. Our transgenic (tg) animal models are most suitable to study early AD pathological events, as the pathology evolves in a well-staged manner, starting with intracellular A accumulation and ending with plaque deposition. OBJECTIVE: To determine the occurrence of key inflammatory markers and to look for signs of nerve growth factor (NGF) dysmetabolism at preplaque and postplaque stages in tg models of AD-like amyloid pathology and in human AD brains. METHODS: We used our own tg lines (mice and rat), high-quality human brain material and applied neurochemical and immunohistochemical experimental approaches. RESULTS: In both tg models, we observed an intracellular accumulation of oligomeric A in cortical and hippocampal pyramidal neurons. This coincided with an upregulation of key inflammatory markers (iNOS, MHCII, COX-2) and a recruitment of microglia towards A -burdened neurons. Using human AD brains, we showed alterations in the NGF metabolic pathway, which were mirrored in our tg rat model at early and late stages of amyloid plaque generation. CONCLUSION: A proinflammatory process and, consequently, the deregulation of the NGF metabolic pathway could be amongst the earliest pathological events in the progression of AD.

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Preplaque ('Preclinical') Aβ-Induced Inflammation and Nerve Growth Factor Deregulation in Transgenic Models of Alzheimer's Disease-Like Amyloid Pathology

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Key Words

Alzheimer's disease · Intracellular amyloid-β oligomers · Inflammation · Nerve growth factor · Inducible nitric oxide synthase · Matrix metalloproteinase 9 · Minocycline · Basal forebrain cholinergic neurons

Abstract

Background: Alzheimer's disease (AD) neuropathology likely begins decades before clinical symptoms are manifested. Investigations on the early stages of the amyloid pathology are crucial for the discovery of diagnostic biomarkers or new therapeutic targets. Our transgenic (tg) animal models are most suitable to study early AD pathological events, as the pathology evolves in a well-staged manner, starting with intracellular Aβ accumulation and ending with plaque deposition. ***Objective:*** To determine the occurrence of key inflammatory markers and to look for signs of nerve growth factor (NGF) dysmetabolism at preplaque and postplaque stages in tg models of AD-like amyloid pathology and in human AD brains. ***Methods:*** We used our own tg lines (mice and rat), high-quality human brain material and applied neurochemical and immunohistochemical experimental approaches. ***Results:*** In both tg models, we observed an intracellular accumulation of oligomeric Aβ in cortical and hippocampal pyramidal neurons. This coincided with an upregulation of key inflammatory markers (iNOS, MHCII, COX-2) and a recruitment of microglia towards Aβ-burdened neurons. Using human AD brains, we showed alterations in the NGF metabolic pathway, which were mirrored in our tg rat model at early and late stages of amyloid plaque generation. ***Conclusion:*** A proinflammatory process and, consequently, the deregulation of the NGF metabolic pathway could be amongst the earliest pathological events in the progression of AD.

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Introduction

It is becoming increasingly clear that Alzheimer's disease (AD) neuropathology starts decades before the first clinical symptoms are manifested. Unfortunately, there are not, as yet, definitive biomarkers to predict the evolution of individuals from a noncognitively impaired (NCI) status to mild cognitive impairment (MCI) and AD [1]. In addition, the study of human postmortem brains does not allow the identification of predictive biomarkers – even when the full characterization of the neuropathology and cognitive status is available – as there is no unquestionable evidence that a given subject categorized as NCI would necessarily evolve to MCI or AD. For this, new insights on the earliest stages of the amyloid pathol-

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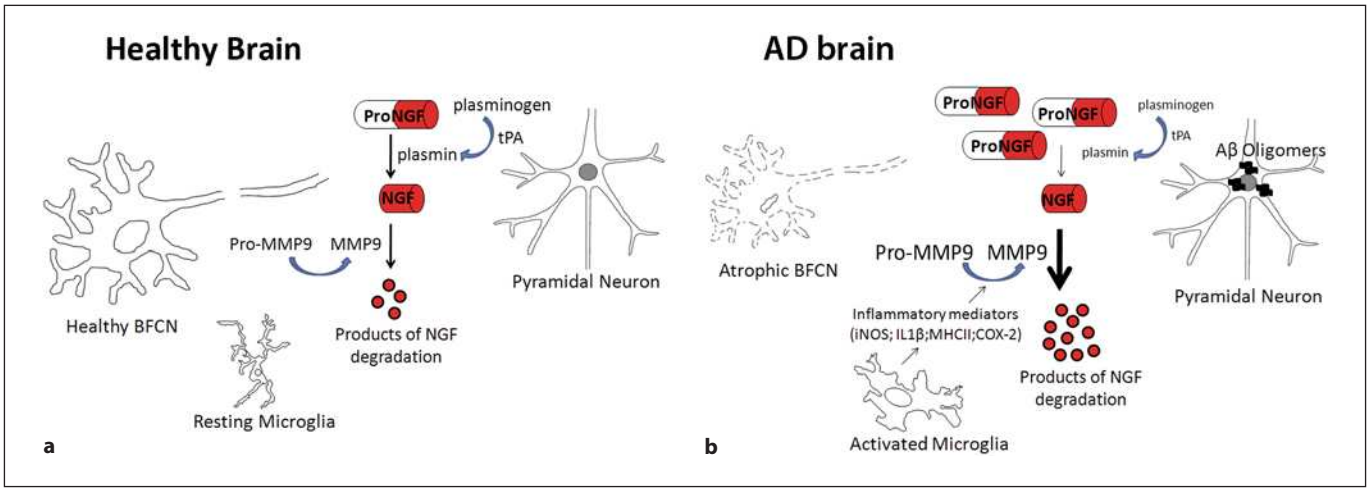

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Fig. 1. Schematic representation of the NGF metabolic pathway in normal brains and in AD. **a** In normal brains, proNGF is released to the extracellular space by cortical pyramidal neurons along with the converstases and zymogens necessary for its processing to mNGF and its degradation. Briefly, plasminogen is converted to plasmin by tissue plasminogen activator (tPA) and plasmin cleaves proNGF into its mature form. The NGF molecules that are not retrogradely transported to the basal forebrain by projecting cholinergic neurons are degraded by MMP9. BFCN depend throughout life on the continuous endogenous supply of NGF for phenotype maintenance. **b** In AD, the lack of trophic support to BFCN can be partly explained by a dramatic dysregulation in the expression and activity of the members of the NGF metabolic pathway. The presence of intracellular Aβ oligomers unleashes a proinflammatory reaction that negatively impacts on the regulation of the NGF metabolic pathway. Plasminogen, tissue plasminogen activator and plasmin levels are reduced, explaining the paradoxical elevation of the NGF precursor in the presence of BFCN atrophy. The degradation of endogenous NGF levels is exacerbated, as MMP9 levels and activity are highly increased.

ogy are pivotal to the discovery of predictive biomarkers and new therapeutic targets.

The above objectives could theoretically be attained by an in-depth investigation of the preclinical stages of individuals carrying familial AD genes. This is not an easy task given the limited number of such patients and the time required for solid conclusions. In this regard, transgenic (tg) animal models of the AD-like amyloid pathology are most suitable to unravel early AD pathological events.

Materials and Methods

We utilized the McGill-Thy1-APP mouse [2] and the McGill-R-Thy1-APP rat [3] tg models of the AD-like amyloid pathology. Both models carry the human amyloid precursor protein (APP) transgene with familial AD mutations, resulting in extracellular plaque deposition, dystrophic neurites and a periplaque inflammatory process. We investigated the occurrence of key inflammatory markers and the status of the proteins involved in the metabolism of nerve growth factor (NGF) using a combination of neurochemical and immunohistochemical approaches as described previously [3, 4]. Whenever possible we have investigated biochemical alterations of the above markers in human AD brains from the Netherlands Brain Bank and from the Religious Orders Study, Rush Medical Center (Chicago, Ill., USA).

Results and Discussion

We investigated features of the early AD-like amyloid pathology in our tg animals on the understanding that preplaque and the early extracellular amyloid plaque phase would clearly correspond to human preclinical stages, as has been eloquently highlighted by Ashe and Zahs [5]. We observed that prior to the appearance of amyloid plaques there is an intracellular accumulation of Aβ oligomeric molecular forms in cortical and hippocampal neurons. The systematic time-dependent analysis of the occurrence of intracellular Aβ-immunoreactive material, as investigated with an Aβ oligomer-specific monoclonal antibody (Nu1) [6], and with a peptide-oligomeric conformation-specific polyclonal antibody (OC) [7], suggested an evolution of this material towards a progressive intraneuronal accumulation of Aβ oligomers and later appearance of fibrillar Aβ material, the latter largely disappearing as amyloid plaques emerged [2]. The incremental intraneuronal accumulation of Aβ-immunoreactive oligomeric species was coincidental with an upregulation of some key markers of inflammation such as iNOS, MHCII, IL-1β and COX2 [4, 8] and mobilization of resident microglial cells to-

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wards Aβ-burdened neurons of the cerebral cortex and hippocampus [4].

Our laboratory identified the modality of CNS release of NGF; the precursor proNGF but not mature NGF (mNGF) is released in an activity-dependent manner. Furthermore, we described the metabolic pathway responsible for its maturation and degradation [9]. Therefore, we were interested in establishing whether an alteration of this pathway could explain the well-known vulnerability of NGF-dependent basal forebrain cholinergic neurons (BFCN). The existence of BFCN atrophy in AD brains in the absence of detectable changes in the synthesis of NGF [10] and elevated levels of proNGF [11] results in an apparent contradiction. We therefore investigated the levels and activity of the members of the NGF metabolic cascade in tg models and AD brains. In AD, we observed increased proNGF levels, decreased levels of plasminogen and tissue plasminogen activator and consequently of plasmin, the protein responsible for the conversion of proNGF to mNGF [12]. Such a defect would be sufficient to explain the paradoxical elevation of proNGF as well as the cholinergic atrophy resulting from this trophic disconnection. However, in AD, the situation is further aggravated by the elevation of matrix metalloproteinase 9 (MMP9), the enzyme responsible for mNGF degradation [12]. Interestingly, these biochemical changes are even present at very early stages of the AD pathology, as it has been observed that proNGF is already elevated in MCI [13]. Furthermore, we have also reported an elevation of the levels and zymographic activity of MMP9 in MCI; changes that correlated with cognitive deterioration [14].

We have recently found indications of a similar deregulation of the CNS NGF pathway in our McGill tg rat model. At late stages of the amyloid pathology, we have observed an increase in proNGF levels and MMP9 activity. Interestingly, elevated levels of proNGF were also present at early stages of amyloid plaque generation [15, 16].

Based on our studies in tg models, inflammation and NGF deregulation are early, connected components of the AD amyloid pathology (fig. 1). Supporting this view, we have seen that injecting Aβ oligomers in the hippocampus of naïve rats is sufficient to unleash an inflammatory process as well as an elevation of proNGF [12]. The application of the CNS anti-inflammatory agent minocycline is sufficient to correct both alterations at very early stages in mice tg models [12, 17, Ferretti et al., in preparation].

Conclusions

In brief, we have found a proinflammatory process at the earliest 'preclinical' stages of the AD-like amyloid pathology in tg models. We hypothesize that this early and previously unnoticed inflammation could unleash the deregulation of the NGF metabolic pathway; a process which will ultimately lead to CNS BFCN atrophy [18]. These pathological events might be amongst the earliest in the progression of AD and they could offer new insights for the identification of potential diagnostic biomarkers or pharmacological targets for AD prevention.

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References

1 Hansson O, et al: Association between CSF biomarkers and incipient Alzheimer's disease in patients with mild cognitive impairment: a follow-up study. Lancet Neurol 2006; 5:228–234.
2 Ferretti MT, et al: Transgenic mice as a model of pre-clinical Alzheimer's disease. Curr Alzheimer Res 2011;8:4–23.
3 Leon WC, et al: A novel transgenic rat model with a full Alzheimer's-like amyloid pathology displays pre-plaque intracellular amyloid-beta-associated cognitive impairment. J Alzheimers Dis 2010;20:113–126.
4 Ferretti MT, et al: Intracellular Aβ-oligomers and early inflammation in a model of Alzheimer's disease. Neurobiol Aging 2011, E-pub ahead of print.
5 Ashe KH, Zahs KR: Probing the biology of Alzheimer's disease in mice. Neuron 2010; 66:631–645.
6 Lambert MP, et al: Monoclonal antibodies that target pathological assemblies of Abeta. J Neurochem 2007;100:23–35.

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7 Kayed R, et al: Fibril specific, conformation dependent antibodies recognize a generic epitope common to amyloid fibrils and fibrillar oligomers that is absent in prefibrillar oligomers. Mol Neurodegener 2007;2:18.
8 Hanzel CE, et al: Early inflammatory process in a novel transgenic rat model of Alzheimer's disease. 8th Int Brain Res Organization World Congr, Florence, 2011.
9 Bruno MA, Cuello AC: Activity-dependent release of precursor nerve growth factor, conversion to mature nerve growth factor, and its degradation by a protease cascade. Proc Natl Acad Sci USA 2006;103:6735–6740.
10 Goedert M, et al: Nerve growth factor mRNA in peripheral and central rat tissues and in the human central nervous system: lesion effects in the rat brain and levels in Alzheimer's disease. Brain Res 1986;387:85–92.
11 Fahnestock M, et al: The precursor pro-nerve growth factor is the predominant form of nerve growth factor in brain and is increased in Alzheimer's disease. Mol Cell Neurosci 2001;18:210–220.
12 Bruno MA, et al: Amyloid beta-induced nerve growth factor dysmetabolism in Alzheimer disease. J Neuropathol Exp Neurol 2009;68:857–869.
13 Peng S, et al: Increased proNGF levels in subjects with mild cognitive impairment and mild Alzheimer disease. J Neuropathol Exp Neurol 2004;63:641–649.
14 Bruno MA, et al: Increased matrix metalloproteinase 9 activity in mild cognitive impairment. J Neuropathol Exp Neurol 2009;68:1309–1318.
15 Iulita MF, et al: Studies on the NGF metabolism in a new transgenic rat model of Alzheimer's disease-like amyloid pathology and in Down's syndrome cortical neurons. 40th Annu Meet Soc Neurosci, San Diego, 2010.
16 Iulita MF, et al: Brain alterations in nerve growth factor metabolism in a novel rat transgenic model of Alzheimer's disease. 8th Int Brain Res Organization World Congr, Florence, 2011.
17 Ferretti MT, et al: Minocycline corrects early, pre-plaque neuroinflammation and inhibits BACE in a transgenic model of AD-like amyloid pathology. Alzheimer's Assoc Int Conf Alzheimer's Disease, Paris, 2011.
18 Ferretti MT, Cuello AC: Does a pro-inflammatory process precede Alzheimer's disease and mild cognitive impairment? Curr Alzheimer Res 2011;8:164–174.

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